

The Management of Patients With Malignant Lymphoma

JUSTIN J. STEIN, M.D., *Los Angeles*

■ *The prognosis of patients with malignant lymphoma discovered in the localized state and adequately treated is excellent. The prognosis for patients with malignant lymphoma, in general, is much more favorable than is generally recognized.*

Radiation therapy is the treatment of choice for localized malignant lymphoma. Radiation therapy and chemotherapy can produce excellent palliation in patients with advanced disease and long-term survival in many of them.

THE MALIGNANT LYMPHOMAS originate from the primitive mesenchyme. They occur universally, involve individuals of both sexes and all ages and may originate in most of the organs of the body.

Gall⁶ defined malignant lymphoma as "an uncontrolled neoplastic overgrowth of one or another of the cellular inhabitants of lymph node tissue." He said further that it "is usually multinodal in distribution although often with regional limitation, and may on occasion arise in extranodal sites (viscera, skin, bone)."

A classification of the malignant lymphomas for treatment-planning is as follows:

- Lymphosarcoma
- Reticulum cell sarcoma
- Giant follicular lymphoma
- Hodgkin's disease

Jackson and Parker⁷ have classified Hodgkin's disease into Hodgkin's paraganuloma, Hodgkin's granuloma and Hodgkin's sarcoma.

The cause of the malignant lymphomas is unknown. Because of the common origin of these tumors from the primitive mesenchyme, the growth may appear to be a variant of one type into another.

Diagnosis

The diagnosis of malignant lymphoma is based upon the following criteria, as indicated:

- A complete history and physical examination.
- Biopsy of an entire lymph node whenever possible. It should be remembered that if lymph nodes are enlarged in several accessible superficial areas, the removal of a node from the groin or from the axilla is certainly less likely to be rewarding than the excision of an enlarged node from the neck. Because of repeated chronic infections or trauma to the extremities, the inguinal and axillary lymph nodes may often be enlarged.
- A roentgenogram of the chest, and, when indicated, a roentgenographic study of the gastrointestinal tract and of certain skeletal areas.
- A careful ear, nose and throat examination to rule in or out malignant lesions of other types.
- Peripheral blood studies and, if necessary, puncture of the sternum or ilium for bone marrow studies.
- Liver and kidney function tests and intravenous pyelograms when indicated.
- Lymphangiographic study may be done. This procedure will be especially helpful to determine the stage of the disease.

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Professor of Radiology, UCLA Center for the Health Sciences, Los Angeles.

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Basic Principles of Therapy

Some basic principles to be considered when deciding whether to use radiation therapy in the treatment of cancer are as follows:

- The cell type of the tumor to be treated.
- The anatomic location of the tumor and the extent or stage of the disease.
- Whether cure is possible or if only palliation is to be achieved.
- If cure is possible, whether to use surgical or radiation therapy singly or in combination.
- Knowledge of the use of other treatment measures, such as chemotherapy and hormone therapy, and the indications for them.
- A thorough knowledge of the life history of the disease to be treated.

It should be noted further that the knowledge, training and judgment of the therapist is more important than the type of equipment or the drugs to be used.

Radiosensitivity

The malignant lymphomas as a group are radiosensitive. The most sensitive cells in the peripheral blood are lymphocytes, polymorphonuclear leukocytes and erythrocytes, in that order. Lymphoid tissue is very radiosensitive. Often lymphomas will regress after a tumor dose of 500 to 1,000 rads; however, recurrences are more frequent and at shorter intervals.

Noetzi and Sheline¹⁴ made a study of local recurrence in lymph nodes irradiated for Hodgkin's disease. Their data indicated that in patients with this disease observed up to two years after radiation therapy, lymph node enlargement recurs more frequently and sooner after treatment with low doses than with higher doses. This relationship continued to tumor doses of approximately 2,000 rads.

Radiosensitivity and radiocurability are not necessarily synonymous; however, the possibilities for prolonged survival and a relatively high percentage of cure place the malignant lymphomas in a favorable group for radiation therapy.

Therapy Equipment

The majority of malignant lymphomas have been treated by conventional x-ray therapy equipment (200 to 300 kv).

Since cobalt 60 and other types of megavoltage equipment have become more widely available, there has been a trend to use them in the treatment of the more deeply located lesions.

The advantages of megavoltage therapy are the sparing of the skin, greater depth doses can be more easily obtained, the radiation beam can be more precisely determined with less back and side scatter, and the radiation is absorbed more homogeneously throughout the entire treatment area because the difference in the rate of absorption in bone, fat and muscle is less than with conventional x-ray. Because of this more equal absorption in all tissues the dosage can be more accurately determined in the head and neck and pelvic and retroperitoneal regions where bone, soft tissues and air spaces are present.

It must be emphasized that it is not the radiation per se or the type of equipment that determines the outcome for the patient; what is essential is that the physician who is employing radiation therapy be well trained in its use, that he have an excellent knowledge of the life history of the disease to be treated and that he know the limitations of his own specialty and that of other specialties. He must also have an optimistic outlook, for too often a defeatist attitude will lessen the possibility of favorable outcome.

Hodgkin's Disease

In order to plan the treatment for Hodgkin's disease, it is necessary to stage or classify the disease as to its extent. The method used at the Toronto General Hospital is as follows¹⁶:

Stage I—Involvement of a single site or lymphatic region.

Stage II—Involvement of two or three proximal lymphatic regions:

- (a) Without symptoms of generalized disease;
- (b) With symptoms of generalized disease.

Stage III—Involvement of two or more distant lymphatic regions.

Boden⁵ advocated the treatment of all localized cases of lymphosarcoma and Hodgkin's disease according to the following principles:

- "1. The zone to be treated must extend five cm wide in every direction of the lesion or of the lymph node group if the lesion lies in lymph nodes.
- "2. The whole of the anatomical lymph node

group or groups associated with a lesion must be included in the zone to be treated.

"3. The zone must be irradiated as one undivided volume."

Using the above principles for treatment, Boden obtained a crude survival rate of 53 per cent for localized Hodgkin's disease and of 50 per cent for localized lymphosarcoma. His survival rate for five years for 112 patients with Hodgkin's disease was 26 per cent, and for 95 patients with lymphosarcoma it was 28 per cent.

The therapy of Hodgkin's disease has been very confusing. Often in the past only moderate doses of radiation therapy were given to patients with localized disease and the contiguous areas were seldom treated. The accepted opinion was that the disease was of multicentric origin and that the possibility of cure was minimal. Often patients with involvement of the mediastinal lymph nodes have been treated with small doses and not long afterward the nodes enlarged again and symptoms recurred. Many physicians have had a defeatist attitude toward the prognosis in patients with malignant lymphomas and some have expressed doubt that involvement is ever unicentric in this disease. Yet many of the patients with localized disease are young and have few if any systemic symptoms, and thorough treatment of the involved area, with prophylactic radiation therapy to adjacent lymphatic drainage areas, has certainly proven to be worthwhile.

Not often (until the terminal stage of the disease) are there recurrences in areas that have been heavily irradiated. In this regard it should be noted that it may take three months or more for the full effect of the therapy to be realized; hence one should not be in a hurry to re-treat an area because of enlargement of nodes.

If the disease is localized and radical operation is done, radiation therapy should not be given. The decision to be made is between adequate radiation therapy and surgical removal.

Vaeth¹⁹ studied 45 cases of Hodgkin's disease in which mediastinal recurrence followed radiation therapy. This study confirmed the observation that failure is usually due to insufficient tumor dose or too small a field of treatment. He held that the entire bloc of mediastinal lymph nodes should receive at least 3,500 r tumor dose and that when adjoining fields are treated there should be no untreated areas between the fields.

Peters¹⁶ advocated a dose of approximately

3,500 rads in three weeks to the involved area and 2,500 rads in three weeks to contiguous areas for Stages I and II.

Kaplan's⁹ experience indicated a significant superiority of the intense treatment method, which consists of tumor doses of 3,500 to 4,000 rads in three to four weeks for localized Hodgkin's disease. The tumor dose is usually given to fields which include clinically uninvolved contiguous lymph node chains, with or without concomitant nitrogen mustard treatment.

Crosbie⁴ recommended a tumor dose of 3,500 to 4,000 r when Hodgkin's disease is limited to a single set of lymph nodes. When the disease involves two or three contiguous lymph node groups, a similar tumor dose is given and, in addition, the uninvolved contiguous lymph node groups are prophylactically treated.

Peters¹⁵ reported long-term survival rates of 319 patients with Hodgkin's disease treated by radiation in the period 1928-54 as follows:

Stage	Number of Patients	Survival			
		5 Year	10 Year	15 Year	20 Year
I	70	71%	50%	40%	40%
IIa	51	88%	66%	50%	50%
IIb	63	22%	10%	3%	0%
III	135	14%	5%	4%	2%
All Stages ...	319	40%	26%	20%	18%

Five-year survival rates for 316 patients with Hodgkin's disease reported by Molander and Pack¹¹ were 37.5 per cent for those with Stage I disease, 27.5 per cent for Stage II and 14.8 per cent for Stage III. These investigators were of the opinion that radiation therapy is the principal and most effective form of treatment for the majority of patients with malignant lymphoma.

Hodgkin's Disease in Children

In children Hodgkin's disease confined to lymph nodes in one region may be curable by radiation therapy the same as in adults. Kelly¹⁰ reported that in 32 of 42 cases in children under 15 years old, enlargement of cervical lymph nodes was the presenting symptom, and it was the main symptom in 27 of 28 patients with localized disease. Twelve of the 42 patients were alive and well five years after radiation therapy and eight of the 30 who died survived at least five years.

Pitcock¹⁷ and associates in a study of 46 children with Hodgkin's disease, all but one treated principally with irradiation, found that 60 per cent

with localized disease lived five years and 35 per cent for ten years. Eight of the 46 (17 per cent) were still alive from five to 33 years after the diagnosis, which was made by biopsy. These investigators found that initial doses of radiation therapy less than 1,800 r in Stage I (localized) cases did not completely eradicate the disease and retreatment of the lymph node area was necessary.

Peters and Middlemiss¹⁶ reported the five-year survival of 11 children under 11 years of age with Hodgkin's disease treated by radiation therapy as 55 per cent and for 27 patients with ages ranging from 11 to 20 years as 52 per cent.

While the disease is more common in males, the prognosis is more favorable in females.

No data has been presented to show that radical operation alone will produce better results than radiation therapy. Operation usually is limited to the taking of an intact large lymph node for histological study.

Malignant Lymphoma Other Than Hodgkin's Disease

If a patient has localized lymphosarcoma or reticulum cell sarcoma, the same kind of therapy as that used for Hodgkin's disease should be carried out. The prognosis is better, however, with Hodgkin's disease and the lesions grow more slowly.

Fuller⁵ found that tumor doses of approximately 3,000 to 5,000 rads are necessary for permanent control of malignant lymphomas of Stage I and Stage II. She expressed the opinion that reticulum cell sarcomas generally require a tumor dose of about 5,000 rads. The lymphocytic lymphosarcomas are more radiosensitive. She administered prophylactic radiation therapy to the supraclavicular fossa when the disease originated in the mediastinum or the axilla. Of a series of 278 patients with malignant lymphomas, 38.4 per cent survived for five years.

The results of treatment of 567 patients with malignant lymphoma other than Hodgkin's disease are reported by Molander and Pack¹¹ as follows: Five-year survival for Stage I was 35 per cent, for Stage II 25 per cent, and for Stage III 22 per cent.

Chemotherapy

There is no indication for the use of chemotherapy in the treatment of localized (Stage I) Hodgkin's disease or of Stage IIa. Patients in

Stage IIb who have systemic symptoms might be helped by chemotherapy in addition to irradiation. The initial approach to the therapy of patients with Stage III involvement could be by chemotherapy, with irradiation used for residual lesions. The chemotherapeutic agents most commonly used in the treatment of the malignant lymphomas are nitrogen mustard (HN₂), cyclophosphamide (Cytoxan®) and thio-tepa. The chemotherapeutic agents are palliative, not curative.

Radiation therapy alone or with chemotherapy can produce effective palliation of hepatosplenomegaly, bone lesions, paraplegia, and symptoms caused by involvement of other organs.

Gastrointestinal Malignant Lymphoma

Jordan and coworkers,⁸ in a review of the English literature on gastric malignant lymphomas in the period 1939-1954, collected reports of 406 cases. Detailed analysis was available on 373 cases of primary lymphoma of the stomach. Among patients who survived resective operation, the five-year survival rate was 42.6 per cent. In comparing the end results of the treatment of primary lymphomas of the stomach with gastric carcinoma, they concluded that the prognosis for gastric lymphoma was twice as good as the best reported five-year survival rates for gastric carcinoma. They recommended radiation therapy for all patients with lymphoma who had any residual disease after operation.

A survival rate of 42 per cent in 24 patients who had operation for primary gastric malignant lymphoma was reported by Warren and Littlefield.⁷⁰

Cook and Corbett⁸ in reporting on 1,014 cases of malignant lymphoma noted that 6.5 per cent of the cases were primary in the gastrointestinal tract with the majority being lymphosarcomas. The absolute five-year survival rate for 42 cases of lymphosarcoma and reticulum cell sarcoma originating in the gastrointestinal tract and mesentery was 35.7 per cent. Cook and Corbett expressed the opinion that "while surgery provides a valuable adjunct in the management of their patients, roentgen therapy remains the indispensable treatment for both localized and generalized lymphoma."

Twenty-nine per cent of 21 patients with primary gastric malignant lymphomas treated at the Memorial Hospital for Cancer and Allied Diseases, New York City, lived for five years or

longer. McNeer,¹² who reported on this series, commented that "although primary gastric Hodgkin's disease has been described and reported by some authors, the senior pathologists at Memorial Hospital do not believe that Hodgkin's granuloma ever appears as a primary gastric tumor." Lymphocytic lymphosarcoma and reticulum cell sarcoma were the lymphomatous types reported by McNeer.

In a series of patients with malignant lymphomatous involvement of the small bowel reported upon by McPeak,¹³ the one patient with lymphosarcoma of the duodenum who was treated surgically did not survive five years. Radiation therapy was used before or after operation in eight patients with jejunal lymphosarcoma and four of them had some palliative effect. Chemotherapy, used in three patients, was without benefit. There were no long-term survivors. Of 18 patients with lymphosarcoma of the ileum, 15 had postoperative radiation and in five of them it had some palliative effect. Of seven patients who received chemotherapy, three had some transient effect. Three patients with ileal lymphosarcoma who were treated with irradiation after operation were alive and well for five years.

Ullman and Abeshouse¹⁸ collected reports of 109 cases of lymphosarcoma of the intestines and found that in only 32 of them did the lesion originate in the large bowel.

It is often difficult for a surgeon to differentiate accurately between a gastrointestinal malignant lymphoma and a primary carcinoma solely from visual inspection and palpation. Biopsy studies should always be made because if the lesion is considered to be inoperable, radiation therapy may at least be palliative and possibly curative. In any case in which resection of the lesion is considered not to have been adequate or disease is present in the regional lymph nodes, radiation therapy should be carried out.

Hodgkin's Disease and Pregnancy

Considerable scientific evidence has been accumulated to indicate that the course of Hodgkin's disease is not influenced by pregnancy nor the fetus adversely affected. For this reason therapeutic abortions have not been recommended.

All therapy should be avoided during the first trimester of pregnancy because of the potential danger of fetal injury. When therapy of any type is given, the possibility of harmful effects to the

fetus should be considered. I treated one patient with Hodgkin's disease who had four children in the 12 years she lived after diagnosis of Hodgkin's disease. Fortunately at times when the disease became active during pregnancy, the affected area was such that treatment could be postponed until after delivery.

Becker and Hyman¹ determined the amount of radiation which would reach the fetus from internal scatter. When a tissue dose of 1,000 r was delivered to the mid-mediastinum through a 15 × 15 cm field, the internal scatter to the fetal region was 9.0 for 250 kv radiation; 2.9 r for cobalt 60; and less than 0.1 r for rays from the 22.5 Mev betatron. The external scatter which could be reduced by shielding of the abdomen by appropriate material was found to be less than 0.1 r for all three treatment modalities.

Radiotherapy Division, U.C.L.A. Medical Center, Los Angeles, California 90024.

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